(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 019 403**
A2

(12) # EUROPEAN PATENT APPLICATION

(21) Application number: 80301464.6

(22) Date of filing: 02.05.80

(51) Int. Cl.³: A 61 K 9/22

(30) Priority: 10.05.79 US 37981

(43) Date of publication of application:
26.11.80 Bulletin 80/24

(84) Designated Contracting States:
BE IT

(71) Applicant: AMERICAN HOSPITAL SUPPLY CORPORATION
One American Plaza
Evanston, IL 60201(US)

(72) Inventor: Berger, Kenneth L.
1224 Brangwyn Way
Laguana Beach California(US)

(72) Inventor: Brake, Jon M.
720 W.Foothill, Apt.8
Monrovia California(US)

(72) Inventor: Deindoerfer, Fred H.
9221 Encino Avenue
North Ridge California(US)

(72) Inventor: Bankert, Charles Sem
126 26th Street
Newport California(US)

(74) Representative: Seaborn, George Stephen et al,
c/o Edward Evans & Co. Chancery House 53-64 Chancery Lane
London WC2A 1SD(GB)

(54) **Hydroxyalkyl-starch drug carrier and method of administering a biologically active compound to an animal.**

(57) A composition is disclosed for the controlled release administration of a biologically active compound to an animal, comprising a combination of the biologically active compound and hydroxyalkyl starch.

EP 0 019 403 A2

Croydon Printing Company Ltd.

TITLE MODIFIED
see front page

Hydroxyalkyl Starch Drug Carrier

BACKGROUND OF THE INVENTION

This invention relates to compositions and a method for administering biologically active substances to an animal in a controlled release formulation. More particularly, the invention relates to a polymeric carrier for such biologically active substances which has a low order of toxicity and long term persistence in the body.

Various methods for administering drugs in controlled release formulations, e.g. sustained release or delayed release, have been proposed. A concept which has been of general interest in the field involves administration of drugs as derivatives of a polymeric compound. The drug-polymer bond may be labile to be broken by chemical or biological action in vivo thus releasing the drug, or the drug-polymer bond may be substantially stable in the biological system. In the latter types of drug-polymer combinations, the drug remains active on the polymer (or polymer fragments). An advantage of administering drugs as drug-polymer combinations is that the activity of the drug can be controlled over a prolonged period of time, which is often not possible if the drug is administered in a single dose. This prolongation of activity of the drug is dependent on, among other factors, the strength of the polymer-drug bond in the biological system and the rate of metabolism of the polymeric drug carrier. Another advantage of administering drugs in such a manner is that the toxicity of the drug is often reduced. Certain drugs, notably chemotherapeutic agents used for treatment of certain neoplastic diseases, are quite toxic, and methods to reduce their toxicity while maintaining their activity are very desirable. This reduction in toxicity can be a result of a diminution of the effective concentration of the drug in the biological fluid since its release or activity in that fluid occurs over a longer period of time. Frequently, such drugs are metabolized or excreted very rapidly; therefore, to obtain a desired level of activity, the physician must administer relatively large doses. By utilizing a drug-polymer combination, the rate of metabolism or excretion of the drug may be reduced, thus

lowering the actual dose requirements. Another reason that the toxicity may be lower is that a drug which might otherwise undergo undesirable reactions in the body, such as precipitation, complex formation, reaction or degradation, will be prevented or inhibited from such reactions as a result of the polymer-drug combination.

Specific polymers which have been employed as drug carriers are dextran, which is a polysaccharide obtained by the fermentation of sucrose, and various synthetic polymers such as vinyl polymers, polyacrylates and polyamides. Examples of drug-polymer complexes employing dextran are disclosed by Herb, J. R., U.S. Patent 2,885,393, May 5, 1959 and London, E., et al., U.S. Patent Re. 24,642, April 28, 1959. Polymer drug complexes are described generally in an article published in Chemical Week, April 26, 1978, page 45. The following United States patents also describe combinations between polymers and various active components:

3,608,063	3,998,974
3,629,392	4,003,990
3,966,902	4,035,479
3,998,620	

To be useful as a drug carrier, a polymer must be capable of forming a bond or complex with the drug. This capability is dependent on the reactive bonding sites on the drug, and also on the bonding ability of the polymer. In the case of a polymer-drug combination in which the drug is released from the polymer in vivo, the drug and polymer should be connected by a labile bond. In the case of a combination in which the drug remains on the polymer in vivo, the drug-polymer bond must be relatively stable and must not appreciably interfere with the drug activity. The polymer must itself also be substantially non-toxic. Advantageously, the polymer can be modified so that the rate of release of the drug component or its in vivo activity can be accurately controlled. A disadvantage of several of the polymers which have been investigated for this purpose is that they persist in the body. That is, after the drug groups have been released, the polymers are not easily excreted or metabolized to harmless components. Such polymers may, therefore, act as cumulative poisons in the body and defeat their desired function.

Generally, with some exceptions, the use of polymeric drug carriers has heretofore been limited to formulations for oral or topical administration. The toxic effects and the degree of long term persistence

of the polymer in the body are much more significant in parenteral administration. The polymers for oral or topical use are generally unsatisfactory for parenteral use because of these factors. Although dextran has been proposed as a drug carrier for parenteral administration, its use has caused undesirable reactions. In particular, dextran has been found to be antigenic and its use has caused anaphylaxis in patients.

Accordingly, there is a need for a drug carrier polymer which can be easily modified to control the rate of drug release, which inherently has a low order of toxicity, and which, subsequent to drug release, is quickly and substantially excreted from the body or metabolized into harmless components.

SUMMARY OF THE INVENTION

In accordance with the present invention, disclosed is a composition of matter for the controlled release administration of a biologically active compound to an animal, comprising a combination of said biologically active compound and hydroxyalkyl starch.

DETAILED DESCRIPTION OF THE INVENTION

The preferred polymeric drug carrier of this invention is a hydroxyalkyl starch which can be prepared in accordance with the teachings of Hershenson, H., et al., U.S. Patent 3,523,938, August 11, 1970, incorporated herein by reference. The preferred polymeric material is hydroxyethyl starch which is prepared by etherifying waxy starch with ethylene oxide to a predetermined substitution level, and then hydrolyzing the etherified starch to a desired viscosity range.

The Hershenson patent discloses the use of hydroxyalkyl starch as a plasma expander. One of the properties of the polymer which makes it particularly suited for that purpose is that the compound has a high short term persistence in the body, but has a very low long term persistence. Thus, after the polymer has served its function, it is substantially metabolized or excreted from the body, resulting in little, if any, toxic build up.

This property of low long term *in vivo* persistence also enables hydroxyalkyl starch to be advantageously used as a drug carrier. After the drug or biologically active compound has been released in the body, or the

effect thereof has been realized, the polymer is substantially metabolized or excreted. Side effects resulting from the use of the drug carrier are thereby minimized.

The period of prolongation of the activity of the active component is somewhat dependent on the degree of persistence of the polymer. This degree of persistence can, in turn, be controlled by varying the level of substitution of the polymer as described by Hershenson, et al., supra. The greater the degree of substitution, the slower will be the rate of starch hydrolysis in vivo. If the active component is effective while bound to the polymer or to polymer subunits, higher degrees of substitution will prolong such effectiveness by increasing the degree of persistence of the polymer. If shorter action is desired, the degree of substitution can be reduced, resulting in more rapid hydrolysis of the polymer and thus more rapid release of the active component. If the active compound is bound to the polymer by a labile bond, the rate of release of such compound into a body fluid is dependent both upon the level of substitution of the polymeric carrier and upon the strength of the labile bond in vivo.

The preferred level of substitution for the hydroxyalkyl starch will vary, depending upon the particular active component for which the polymer is a carrier, the rate of release or prolongation of activity which is desired, upon the manner of administration. The level will generally fall in the range of from about 0.1 to 3 for oral administration and from 0.1 to 1 for parenteral administration. The preferred range of the level of substitution is from about 1 to 3 for oral administration and from about 0.4 to 0.8 for parenteral administration.

It should be recognized that the hydrolysis of hydroxyalkyl starch is accomplished in the body largely by enzyme action, e.g. by the action of amylase. Thus, the degree of persistence of the polymer is increased as substituent groups thereon are added. As indicated, the level of substitution with hydroxyethyl groups may advantageously be used to control the degree of persistence, but substitution with the biologically active component can also affect the susceptability of the polymer to enzyme action, and thus determine the degree of persistence. In an extreme case, the level of substitution of the polymer may be very low, approaching zero, but because of the presence of active compound on the polymer, the degree of persistence is in the desired range. Because of the effect of the active

compound substituent on the level of persistence, the level of substitution of the polymer and the number of active compound substituents thereon should be determined, based on the degree of persistence desired in each individual case.

The molecular weight of the hydroxyalkyl starch also affects its persistence in the body and the availability of the active component. The molecular weight can be controlled by regulating the degree of acid hydrolysis as taught by Hershenson, et al., supra. For parenteral administration, the molecular weight of the polymer is advantageously between about 1,000 and 500,000, preferably between 10,000 and 200,000. Higher molecular weights are usually employed for oral or topical administration and generally range from about 10,000 to about 2,000,000 and are preferably in a range of from about 200,000 to 450,000.

In accordance with the present invention, it has been discovered that a wide variety of biologically active components can be combined with hydroxyalkyl starch to be released in vivo in a controlled manner, e.g. sustained release or delayed release. As used herein, the term controlled release shall include the actual release of the active compound into the body over a period of time, and shall also include a prolongation or modification of the in vivo activity of such compound although it remains bound to the polymeric carrier or fraction thereof. Such biologically active components can be combined with the polymer directly or through suitable derivatives by chemical bonds, e.g. covalent or ionic bonds, complexation or other means.

Hydroxyalkyl starch, being a substituted polysaccharide, has a plurality of hydroxyl groups which provide useful sites for bonding active compounds. Such bonding is not limited, however, to reactions with the hydroxyl groups. This bonding can be a direct reaction between the active component and the polymer. For instance, if the active component has a carboxylic acid functional group, it can react directly or indirectly with a hydroxyl group on the hydroxyalkyl starch to form an ester. The ester linkage can be easily cleaved in vivo by hydrolysis or enzyme action to release the active compound. In addition to being reacted directly with the polymer, the active compound can be bound to the polymer through a derivative. For example, the following schemes may be employed, where R is an appropriately selected derivatizing agent:

Scheme I

$$\text{Polymer} + R \longrightarrow \text{Polymer} - R$$

$$\text{Drug} + R^1 \longrightarrow \text{Drug} - R^1$$

$$\text{Polymer} - R + \text{Drug} - R^1 \longrightarrow \text{Polymer} - R - R^1 - \text{Drug}$$

Scheme II

$$\text{Polymer} + R \longrightarrow \text{Polymer} - R$$

$$\text{Polymer} - R + \text{Drug} \longrightarrow \text{Polymer} - R - \text{Drug}$$

Scheme III

$$\text{Drug} + R \longrightarrow \text{Drug} - R$$

$$\text{Drug} - R + \text{Polymer} \longrightarrow \text{Drug} - R - \text{Polymer}$$

In each of the above schemes, the derivatizing agents are carefully selected so that the drug or an active drug derivative will be released in vivo, or the activity of the drug will be maintained while it is bound to the polymer. A fourth scheme involves the reaction of a drug precursor ($Drug_p$) with a derivative, followed by reaction with the hydroxyalkyl starch polymer. Upon reaction in vivo, the active drug is released. This scheme is represented below.

$$Drug_p + R \longrightarrow Drug_p - R$$

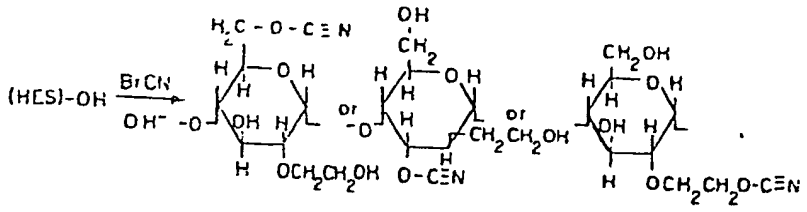
$$Drug_p - R + \text{Polymer} \longrightarrow Drug_p - R - \text{Polymer}$$

$$Drug_p - R - \text{Polymer} \xrightarrow{\text{in vivo}} \text{Drug}$$

Derivatizing agents useful for producing compositions of this invention include substantially any non-toxic compound which will link the active compound to the polymer. Polyfunctional organic compounds are useful for this purpose. Through the above-described reaction schemes, a wide variety of biologically active compounds can be combined with hydroxyalkyl starch to form controlled release formulations.

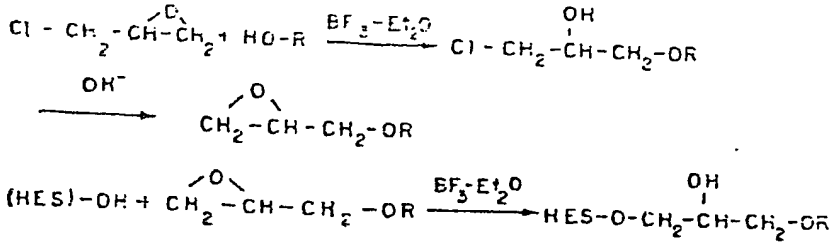
Specific examples of useful modifications to hydroxyalkyl starch are listed below (HES indicates hydroxyethyl starch). For convenience, the reaction involving only one or two hexose units of the hydroxyethyl starch is indicated.

(1)



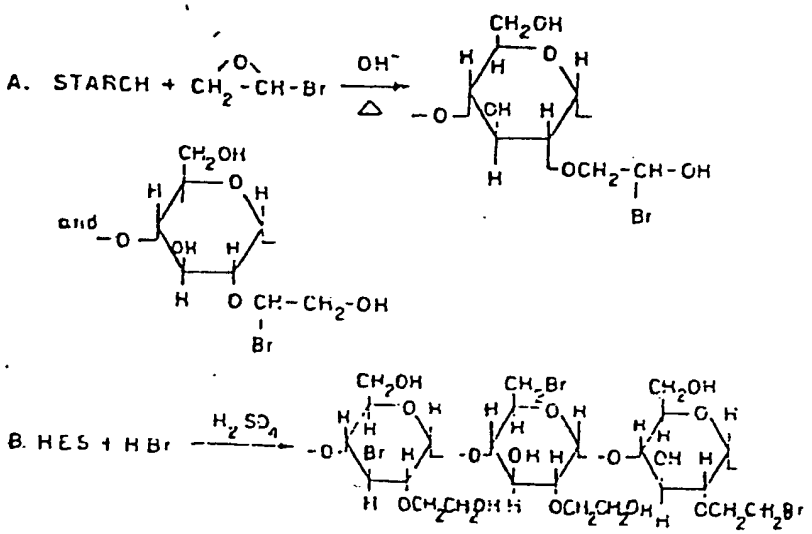
These hydroxyethyl starch derivatives can be reacted with proteins such as the antiviral agent interferon, peptides such as the enkephalins, and amino acids.

(2) Drugs having reactive hydroxyl groups may be derivatized to react with hydroxyethyl starch through stable ether groups in accordance with the following scheme (HO-R represents the drug):

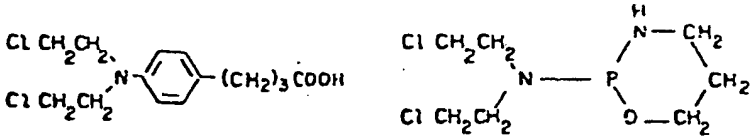


Examples of drugs having such hydroxyl groups include steroids such as hydrocortisone and prednisone and antibiotics such as chloramphenicol.

(3) Hydroxyethyl starch can be halogenated to react in a wide variety of ways. The halogenated derivative may be formed during the preparation of the polymer or by direct halogenation. The following reactions may be employed:



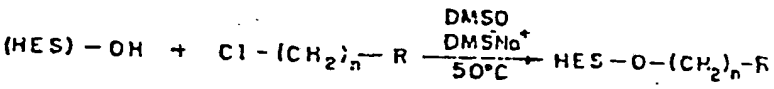
(4) Drugs having alkyl halide functions, such as the antineoplastic agents chlorambucil and cyclophosphamide



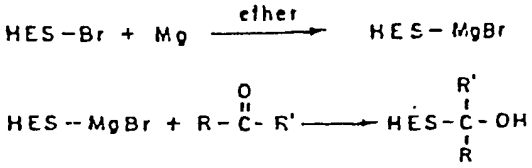
chlorambucil

cyclophosphamide

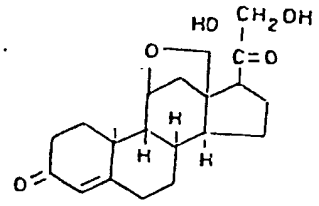
can react with hydroxyethyl starch directly by the following reaction:



(5) Brominated hydroxyethyl starch can be used as a precursor for a Grignard reagent which in turn can be reacted with drugs having aldehyde or ketone functional groups.

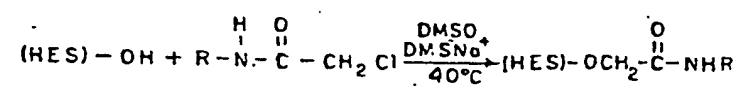


The endocrine antagonist, aldosterone, is an example of a ketone which can participate in the above reaction.



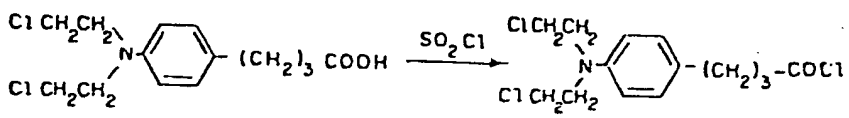
aldosterone

(6) Drugs such as chloramphenicol containing the $-NH-\overset{O}{\overset{\|}{C}}-CH_2Cl$ group can be reacted directly with hydroxyethyl starch by the following reaction:

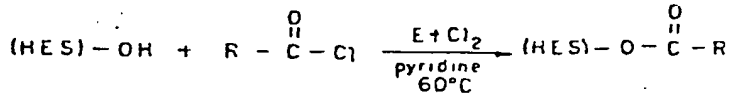


The reaction is therefore useful for any drug having an acetamide group which can be chlorinated, e.g. sulfacetamide and the antimalarial agent DADDS (4, 4' - diacetyl 4, 4' - diaminodiphenylsulfone).

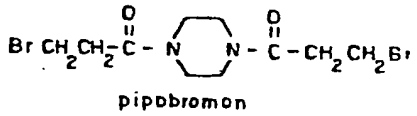
(7) Active compounds having carboxylic acid functional groups can be converted to acyl halides by reaction with thionyl chloride. For instance, chlorambucil can react as follows:



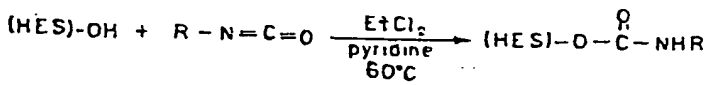
Acyl halides can, in turn, react with hydroxyethyl starch as follows (E + Cl_2 represents 1,2-dichloroethane):



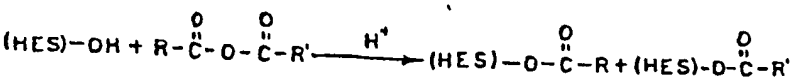
(8) Drugs having alkyl halide groups such as the antineoplastic agent pipobroman can react to form isocyanates which can react with hydroxyethyl starch.



pipobromon

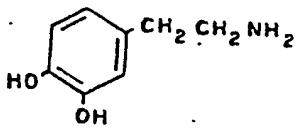


(9) Anhydrides can react with hydroxyethyl starch in the following manner:



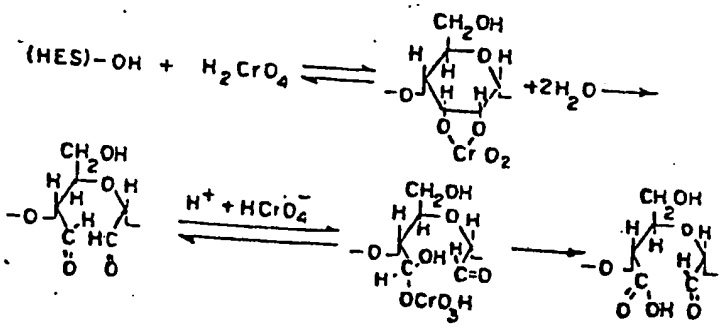
Thus, drugs having carboxylic acid groups, such as vitamin A_2 can be reacted with acetic anhydride to form a mixed anhydride which, in turn, can be so reacted with hydroxyethyl starch.

(10) A wide variety of drugs have amine functional groups. Included in this group are amphetamines and dopamine.

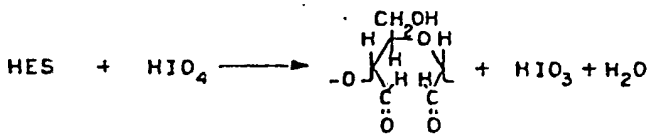


Dopamine

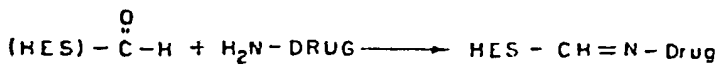
Hydroxyethyl starch can be partially oxidized to form aldehydic compounds which can react with such amine groups to form Shiff base compounds.



another useful oxidation reaction is:



The reaction of aldehydic hydroxyethyl starch with an amine-containing drug is represented as follows:



Certain drugs can be derivatized to contain amine groups which can react with aldehydic hydroxyethyl starch by this scheme.

The method of the present invention is particularly advantageous for administering iron to a patient. The requirements of the body for iron and its therapeutic and prophylactic uses are well documented. Iron salts are generally not administered orally for therapeutic purposes becauses they are poorly absorbed or because they sometimes cause disturbances in the alimentary tract. Therefore, iron is preferably administered parenterally, generally by intravenous injection. Solutions of iron salts are not usually injected directly because they are toxic. A particular problem is that acidic iron forms insoluble precipitates at physiological pH. To overcome these problems, physiologically compatible iron complexes have been developed for parenteral administration. Such complexes have included saccharated iron, complexes of iron with dextrans or dextrins, and complexes of iron with a water swellable polymer. Examples of the latter complexes are described in U.S. Patent 2,885,393, May 5, 1959, and Canadian Patent 991,544.

It has been found that the method of the present invention may be advantageously employed for the administration of iron. Citric acid has a stabilizing effect on the iron and prevents precipitate formation during the reaction. The iron may be bound to the hydroxyalkyl starch through a citric acid derivative, but the exact structure of the iron-polymer

combination is not presently known. The iron is provided by any soluble salt, preferably in the ferric form. An iron salt, such as ferric chloride, and citric acid is combined with an aqueous solution of hydroxyalkyl starch. The solution is advantageously clarified and the pH is raised, e.g. by addition of aqueous ammonia. The resulting solution of iron-hydroxyalkyl starch complex is purified (de-salted) by any convenient means, such as dialysis or ion exchange. The iron-hydroxyalkyl starch complex may be stored as a sterile solution, or may be precipitated and stored in dry form.

The iron-hydroxyalkyl starch compounds of this invention provide iron in safe effective concentrations, and after release of the iron in vivo, the remaining hydroxyalkyl starch is excreted or metabolized. Thus, the compounds can be continuously or repeatedly administered over prolonged periods with few or no side effects attributable to the polymer carrier.

The combinations produced in accordance with the present invention can be administered either orally, parenterally or topically. The low order of in vivo persistence of the hydroxyalkyl starch carrier is, of course, most appreciated during parenteral and particularly during intravenous administration. To the drug-polymer combination may be added conventional pharmaceutical excipients. For instance, intravenous solutions generally contain electrolytes and pH controlling agents to insure that physiological conditions of osmotic pressure and pH exist. Such solutions may also contain nutrients, such as glucose and amino acids as well as other active compounds. Oral formulations may contain conventional excipients, such as flavoring agents and compounds useful for suspending the drug-polymer combination in a liquid or compounds for forming the combination into tablets or capsules. Methods for formulating drugs are well known in the pharmaceutical arts, and the present invention is not limited to particular formulations.

Thus, described herein are novel combinations of hydroxyalkyl starch and biologically active compounds and a method for their administration. Such combinations are characterized by a low long term persistence of the hydroxyalkyl starch in the body and by controlled release of the active compound in vivo.

The invention is further illustrated by the following examples, but is not intended to be limited thereby.

EXAMPLE I

This Example demonstrates the preparation of an iron-hydroxyethyl starch combination.

Hydroxyethyl starch (prepared by the procedure described in Example II of U.S. Patent 3,523,938, and further acid hydrolyzed to a molecular weight of 45,000), 80 g, was dissolved in water to yield 400 ml. of a 20% w/v solution (Solution I). Ferric chloride ($FeCl_3 \cdot 6H_2O$), 125 g, was dissolved in water to yield 250 ml. of a 50% w/v solution (Solution II). Solution I was heated to 60° C with stirring, and Solution II was heated to 40-60° C with stirring. Solution II was slowly added to Solution I with stirring. After addition was complete, granular citric acid, 53.5 g, was slowly added to the mixture with stirring, and the resulting solution was stirred at 60° C for an additional 20 minutes then allowed to cool to room temperature. A 20% aqueous solution of NH_4OH was prepared (Solution III) and slowly added with stirring to the iron-hydroxyethyl starch-citric acid solution until the pH reached 10.4. The solution was then heated to 50° C and stirred for 20 minutes, cooled to room temperature and filtered through a 0.8μ filter. The solution was purified by overnight dialysis against distilled water, and was concentrated to 1100 ml. by vacuum distillation. The iron-polymer combination was precipitated by combining the concentrated solution with 8 liters of acetone. The resulting precipitate was collected by filtration and washed several times with acetone. The precipitate was dried at 80° C in vacuo, yielding 91 grams of dry product having an iron content of 22.7 by weight.

EXAMPLE II

The product from Example I was used for the preparation of an injection solution. The dry product (50 g) was dissolved in warm (50° C) sterile water (100 ml.) by adding the powder slowly to the warm water with stirring. The solution was brought to 175 ml. by the addition of 1.58 g of NaCl and sterile water. The solution was then filtered through a 0.22μ filter and placed in 30 ml. vials. The vials were sterilized for 15 minutes at 250° F and the solution had an iron concentration of 50.5 mg/ml.

EXAMPLE III

The experiment of Example I was repeated in all essential details except that following dialysis and concentration of the solution, the iron-

hydroxyethyl starch was precipitated in cold (5-10° C) acetone, the supernatant discarded and the precipitate washed with one liter of 80% aqueous acetone. The precipitate was allowed to resettle, the supernatant discarded, and the procedure repeated. After the second wash, the precipitate was redissolved in 400 ml. of a 0.7% w/v solution of citric acid. The pH was then adjusted to 8.1 with 4N NH_4OH, and the solution was diluted to 600 ml. with water. The iron-hydroxyethyl starch was reprecipitated and washed with two 1 liter aliquots of 80% acetone. The resulting precipitate was then redissolved as above, reprecipitated, washed with three 1 liter aliquots of 100% acetone and collected by vacuum filtration. The collected precipitate was washed with an additional 1 liter of 100% acetone during filtration and was dried as described in Example I.

EXAMPLE IV

A dry preparation of iron-hydroxyethyl starch was prepared as follows: Hydroxyethyl starch, 10 g, was dissolved in 100 ml. of water. Ferric chloride ($FeCl_3 \cdot 6H_2O$), 20 g, was added to the hydroxyethyl starch solution with stirring, and the resulting solution was heated to 50° C for 15 minutes then heated to 70° C for 30 minutes. The solution was allowed to cool to room temperature and the pH was adjusted from 1.4 to 2.9 by addition of 20% NH_4OH. The resulting solution was then dialyzed against running distilled water overnight. The dialyzed solution was concentrated by rotary evaporation to 80 ml., and the concentrated solution was combined with 1200 ml. of acetone which had been cooled to -20° C by the addition of dry ice, thus causing precipitation of the iron-hydroxyethyl starch. The resulting slurry was allowed to warm to room temperature with stirring, and the precipitate was collected by vacuum filtration; the precipitate being washed with 1 liter of acetone in the process. The precipitate was then dried in a vacuum oven at 90° C overnight to yield 9.8 g of dry product.

EXAMPLE V

The experiment of Example I was repeated in all essential details except that the hydroxyethyl starch starting material was subjected to acid hydrolysis to a molecular weight of 10,000. The solution was purified by

ultrafiltration through a 1000 molecular weight cut off filter to remove free ions. The dialysis step was excluded from the procedure. The experiment yielded 80 g of dry product containing 25.4% iron by weight.

EXAMPLE VI

This example describes the preparation of a hydroxyethyl starch-insulin combination in accordance with the present invention. Hydroxyethyl starch (1 g) in 25 ml. of water is added to a well stirred mixture of CNBr (200 mg) in 100 ml. of water. The pH is maintained at 11 by the addition of 2N NaOH. The activation reaction is continued for 10 minutes and 20 mg of insulin in 20 ml. of 1 M sodium bicarbonate are then rapidly added, lowering the pH. The solution is then stirred overnight in an ultrafiltration cell equipped with an appropriate membrane. The solution is then concentrated and washed with 6 Molal guanidine hydrochloride. When no further free insulin is detected migrating through the membrane, the composition is thoroughly washed with water and concentrated to a final volume of 60-80 ml. The experiment should yield a hydroxyethyl starch-insulin combination useful for the controlled release administration of insulin.

EXAMPLE VII

The experiment of Example VI is repeated in all essential details, except a mixture of amino acids is substituted for insulin. The experiment should yield a hydroxyethyl starch-amino acids combination useful for the controlled release administration of amino acids.

EXAMPLE VIII

The experiment of Example VII is repeated in all essential details except enkephalin (peptide) is substituted for insulin. The experiment should yield a hydroxyethyl starch-enkephalin combination useful for the controlled release administration of enkephalin.

EXAMPLE IX

The experiment of Example I is repeated in all essential details except hydroxypropyl starch is substituted for hydroxyethyl starch. The experiment should yield an iron-hydroxypropyl starch combination.

CLAIMS

1. A composition of matter for the controlled release administration of a biologically active compound to an animal, comprising a combination of said biologically active compound and hydroxyalkyl starch.

2. The composition of claim 1, wherein the biologically active compound to the hydroxyalkyl starch through a chemical bond.

3. The compostiion of claim 1 or 2, wherein the biologically active compound is a drug.

4. The composition of claim 1 or 2, wherein the hydroxyalkyl starch is hydroxyethyl starch.

5. The composition of claim 1 or 2, wherein the biologically active compound is iron.

6. A method for administering a biologically active compound to an animal in a controlled release formulation, which comprises administering to said animal a combination of such biologically active component and hydroxyalkyl starch in a pharmaceutically acceptable dosage form.

7. The method of claim 6, wherein the biologically active compound is bonded to the hydroxyalkyl starch through a chemical bond.

8. The method of claim 6 or 7, wherein the biologically active compound is a drug.

9. The method of claim 6 or 7, wherein the hydroxyalkyl starch is hydroxyethyl starch.

10. The method of claim 6 or 7, wherein the biologically active compound is iron.